Proposed Panel Conclusions and Recommendations on Reference Substances for Validation Studies

Expert Panel Meeting

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Recommend Reference Substance List Reviewers:

- **Robert Scala, Ph.D., *Tuscon, AZ***
- **Ih Chu, Ph.D., *Health Canada***
- **Sidney Green, Ph.D., A.T.S., *Howard University***
- **Yasuo Ohno, Ph.D., D.J.S.T., *National Institute of Health Sciences - Japan***
- **Robert Peiffer, D.V.M., Ph.D., D.A.C.V.O., *Merck Research Laboratories***

BRD Section 12.4: Recommended Reference Substances for Validation Studies

12.4.1 Adequacy and Completeness of the List of Reference Substances (1)

- The list of recommended substances is comprehensive in that the three major groups of products to which the eye is exposed (i.e., industrial chemicals, pharmaceuticals, cosmetics) are represented
- The substances appear to be readily available and in acceptably pure form.
- The range of possible ocular toxicity responses in terms of severity and types of lesions appears to be adequately represented.

12.4.1 Adequacy and Completeness of the List of Reference Substances (2)

- However, while it is recognized the selection of reference substances is in part limited by the availability of *in vivo* reference data, comments and recommendations for the list include:
  - The current list has entirely too many substances and is unwieldy
  - Surfactants are over-represented and correspond to an area where the panel can make selective recommendations
  - The list appears to have too few inorganic substances; more should be added to the list if feasible
  - Classification data for each *in vitro* test should not be included in a list of test substances that are proposed for validating *in vitro* tests; this information should be removed from the list
- Colored substances that might interfere with with the observation of the endpoints should not be included.

12.4.1 Adequacy and Completeness of the List of Reference Substances (3)

- A two-staged study design to Validation Studies: Stage 1
  - During the first stage, a small number of substances from a wide range of chemical classes and spanning the range of severe irritancy should be tested among several laboratories to assess reliability
  - Substances selected for this stage should:
    - Should have an applicable pre-existing *in vivo* database.
    - Cover a broad range of chemical classes that are representative of substances that are most likely to come in contact with the eye (e.g., acids - organic and mineral; alkalis; amines, imines, and amides; alcohols (including polyols); ethers; esters; thiols; halides; quaternary ammonium compounds; N- and S-heterocyclics; and hydrocarbons)
    - Encompass the range of GHS Category 1 responses (i.e., GHS Category 1 subcategories as detailed in Section 12.4 of the BRD)
    - Include a reasonable range of molecular weights, but no formulations, prototypes or products should be included
    - Include only liquid substances as these represent the majority of chemicals in the "real world" that will come in contact with the eye. Using only liquids minimizes the inclusion of additional variables in the first stage of validation

12.4.1 Adequacy and Completeness of the List of Reference Substances (4)

- A two-staged study design to Validation Studies: Stage 2
  - If deemed adequately reliable, an expanded set of substances that would be tested and include multiple representatives of each chemical classes, diverse physicochemical characteristics, and the full range of irritancy responses to assess accuracy.
    - Substances included in this stage should include:
      - Multiple representatives from each chemical class
      - Multiple representatives from each GHS Category 1 subcategory
      - Within each chemical class, compounds of different physical properties (solubility, molecular weight, pH) where feasible
- For all validation studies, Material Safety Data Sheets (MSDS) for the recommended substances should be provided (e.g., a coded MSDS); also do prestudy safety briefing

12.4.2 Additional Criteria in the Selection of Reference Substances

- **Substances known to induce severe lesions, in vivo, in the eyes of humans should be included, even in the absence of rabbit data**